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(54) Title: LOW ADENOSINE ANTI-SENSE OLIGONUCLEOTIDE AGENT, COMPOSITION, KIT AND TREATMENTS

(57) Abstract

A composition comprises a nucleic acid comprising an oligo anti-sense to a target such as polypeptide(s) associated with an ailment afflicting lung airways, genes and mRNAs encoding them, genomic and mRNA flanking regions, intron and exon borders and all regulatory and functionally related segments of the genes and mRNAs encoding the polypeptides, their salts and mixtures. Various formulations contain a requisite carrier, and optionally other additives and biologically active agents. The agent of the invention may be prepared by selecting a target gene(s), genomic flanking region(s), RNA(s) and/or polypeptide(s) associated with a disease(s) or condition(s) afflicting lung airways, obtaining the sequence of the mRNA(s) corresponding to the target gene(s) and/or genomic flanking region(s), and/or RNAs encoding the target polypeptide(s), selecting at least one segment of the mRNA which may be up to 60 % free of thymidine (T) and synthesizing one or more anti-sense oligonucleotide(s) to the mRNA segments which are free of adenosine (A) by substituting a universal base for A when present in the oligonucleotide. The agent may be prepared by selection of target nucleic acid sequences with GC running stretches, which have low T content, and by optionally replacing A in the anti-sense oligonucleotides with a AUniversal base@. The agent, composition and formulations are used for prophylactic, preventive and therapeutic treatment of ailments associated with impaired respiration, allergy(ies) and/or inflammation, such as pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, lung pain, cystic fibrosis, bronchoconstriction, pulmonary hypertension and bronchoconstriction, chronic bronchitis, emphysema, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), ischemic conditions including ischemia itself, and cancers such as leukemias, lymphomas, carcinomas, and the like, e.g. colon cancer, breast cancer, pancreatic cancer, lung cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic metastasis, etc., as well as all types of cancers with may metastasize or have metastasized to the lung(s), including breast and prostate cancer. The present treatment is suitable for administration in combination with other treatments, e.g. before, during and after other treatments, including radiation, chemotherapy, antibody therapy and surgery, among others. The present agent is effectively administered preventatively, prophylactically or therapeutically by itself for conditions without known therapies, or as a substitute for, or in conjunction with, other therapies exhibiting undesirable side effects. The treatment of this invention may be administered directly into the respiratory system of a subject, so that the agent has direct access to the airways and the lungs.

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LOW ADENOSINE ANTI-SENSE OLIGONUCLEOTIDE AGENT, COMPOSITION, KIT & TREATMENTS

BACKGROUND OF THE INVENTION

Field of the Invention

This application relates to an agent comprising anti-sense oligonucleotides of low or no adenosine content. These agents are suitable for the treatment of diseases associated with inflammation, impaired airways, including lung disease and diseases whose secondary effects afflict the lungs of a subject. Examples of these diseases are allergies, asthma, impeded respiration, pain, cystic fibrosis, and cancers such as leukemias, e.g. colon cancer, and the like. The present agent may be administered prophylactically or therapeutically in conjunction with other therapies, or may be utilized as a substitute for therapies that have significant, negative side effects.

Background of the Invention

Respiratory ailments, associated with a variety of diseases and conditions, are extremely common in the general population, and more so in certain ethnic groups, such as African Americans. In some cases they are accompanied by inflammation, which aggravates the condition of the lungs. Asthma, for example, is one of the most common diseases in industrialized countries. In the United States it accounts for about 1% of all health care costs. An alarming increase in both the prevalence and mortality of asthma over the past decade has been reported, and asthma is predicted to be the preeminent occupational lung disease in the next decade. While the increasing mortality of asthma in industrialized countries could be attributable to the increased reliance upon beta agonists in the treatment of this disease, the underlying causes of asthma remain poorly understood.

Anti-sense oligonucleotides have received considerable theoretical consideration as potential useful pharmacological agents in human disease. Their practical application in actual models of human disease, however, has been somewhat elusive. One important impediment to their effective application has been a difficulty in finding an appropriate route of administration to deliver them to their site of action. Many in vivo experiments were conducted by administering anti-sense oligonucleotides directly to specific regions of the brain. These applications, however, necessarily have limited clinical utility due to their invasive nature.

The systemic administration of anti-sense oligonucleotides also presents significant problems, not the least being an inherent difficulty in targeting disease-involved tissues. In contrast, the lung is an excellent target for the direct administration of anti-sense oligonucleotides, and provides a non-invasive and a tissue-specific route. The delivery of anti-sense agents to the lung has been relatively undeveloped.

Adenosine may constitute an important mediator in the lung for various diseases, including bronchial asthma. Its potential role was suggested by the finding that asthmatics respond favorably to aerosolized adenosine with marked bronchoconstriction whereas normal individuals do not. An asthmatic rabbit animal model, the dust mite allergic rabbit model for human asthma, responded in a similar fashion to aerosolized adenosine with marked bronchoconstriction whereas non-asthmatic rabbits showed no response. More recent work with this animal model suggested that adenosine-induced bronchoconstriction and bronchial hyperresponsiveness in asthma may be mediated primarily through the stimulation of adenosine receptors. Adenosine has also been shown to cause adverse effects, including death, when administered therapeutically for other diseases and conditions in subjects with previously undiagnosed hyper reactive airways.

A handful of medicaments have been available for the treatment of respiratory diseases and conditions, although in general they all have limitations. Theophylline, an important drug in the treatment of asthma, is a known adenosine receptor antagonist which was reported to eliminate adenosine-mediated bronchoconstriction in asthmatic rabbits. A selective adenosine A_1 receptor antagonist, 8-cyclopentyl-1, 3-dipropylxanthine (DPCPX) was also reported to inhibit adenosine-mediated bronchoconstriction and bronchial hyperresponsiveness in allergic rabbits. The therapeutic and preventative applications of currently available adenosine A_1 receptor-specific antagonists are, nevertheless, limited by their toxicity. Theophylline, for example, has been widely used in the treatment of asthma, but is associated with frequent, significant toxicity resulting from its narrow therapeutic dose range. DPCPX is far too toxic to be useful clinically. The fact that, despite decades of extensive research, no specific adenosine receptor antagonist is available for clinical use attests to the general toxicity of these agents.

Anti-sense oligonucleotides have received considerable theoretical consideration for their potential use as

pharmacological agents in human disease. Finding practical and effective applications of these agents in actual models of human disease, however, have been few and far between, particularly because they had to be administered in large doses. Another important consideration in the pharmacologic application of these molecules is their route of administration. Many in vivo applications have involved the direct administration of anti-sense oligonucleotides to limited regions of the brain. Such applications, however, have limited clinical utility due to their invasive nature.

The systemic administration of anti-sense oligonucleotides as pharmacological agents has been found to have also significant problems, not the least of which being a difficulty in targeting disease-involved tissues. That is, the necessary dilution of the anti-sense oligonucleotide in the circulatory system makes extremely difficult to attain a therapeutic dose at the target tissue by intravenous or oral administration. The bioavailability of orally administered anti-sense oligonucleotides is very low, of the order of less than about 5%.

There are presently no effective therapies for treating these ailments, or at least no therapies which are effective and devoid of significant detrimental side effects. Accordingly, there is still a need for an agent for the treatment of ailments afflicting the lung airways, including respiratory problems and inflammation, which is highly effective and producing minimal, or entirely devoid of, side effects.

SUMMARY OF THE INVENTION

This invention relates to an agent which comprises an oligonucleotide (oligo) consisting essentially of less than about 15% adenosine (A), which is selected from the group consisting of anti-sense oligonucleotides to mRNAs corresponding to target genes, to genomic flanking regions selected from the group consisting of intron and exon borders, such as the 5' end, the 3' end and the juxta-section between coding and non-coding regions, and to all segments of mRNAs encoding polypeptides associated with ailments afflicting lung airways, combinations thereof, pharmaceutically acceptable salts thereof, and mixtures thereof. The mRNA(s), for example, encode polypeptide(s) such as transcription factors, stimulating and activating factors, interleukins, interleukin receptors, chemokines, chemokine receptors, endogenously produced specific and non-specific enzymes, immunoglobulins, antibody receptors, central nervous system (CNS) and peripheral nervous and non-nervous system receptors, CNS and peripheral nervous and non-nervous system peptide transmitters, adhesion molecules, defensines, growth factors, vasoactive peptides and receptors, and binding proteins; or those mRNA which correspond to an oncogene. The agents is are provided in the form of specific compositions and formulations, with a carrier, and optionally with other therapeutic agents and additives which are typically used for administration by a specific route, e.g. into the respiratory system. The agent is also provided as a capsule or cartridge, and in the form of a kit.

This agent is suitable for the treatment of diseases and conditions associated with impaired respiration and inflammation, including lung diseases, ailments and conditions that have a negative effect on the lungs of a subject. Examples of diseases and conditions, which may be treated preventively, prophylactically and therapeutically with the agent of this invention, are pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, respiratory distress syndrome, pain, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), and cancers such as leukemias, lymphomas, carcinomas, and the like, e.g. colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic metastases, etc., as well as all types of cancers which may metastasize or have metastasized to the lung(s), including breast and prostate cancer. The present agent(s) is (are) also suitable for administration before, during and after other treatments, including radiation, chemotherapy, antibody therapy, phototherapy and cancer, and other types of surgery. Alternatively, the present agent may be effectively administered preventively, prophylactically or therapeutically, and in conjunction with other therapies, or by itself for conditions without known therapies or as a substitute for therapies that have significant negative side effects.

The composition of this invention may be administered by transdermal or systemic routes, including by, but not exclusively, oral, intracavitary, intranasal, intraanal, intravaginal, transdermal, intradermal, intrabuccal, intravenous, subcutaneous, intramuscular, intratumor, intraglandular, by inhalation, intraarterial, intravascular in general, into the ear, intracranial, intrathecal, intraorgan including via a shunt to, for example, the liver or other organs, by implantation and intraocular administration to a human or any other animal, including vertebrates, such as mammals. In a preferred embodiment, the present agents are administered directly into the respiratory

system of a subject, so that the agent has direct access to the lungs, in an amount effective to reduce or inhibit the effect in the lung of the targeted diseases or conditions.

Also part of this invention is a method of producing an anti-sense oligonucleotide consisting essentially of less than about 15% adenosine (A), by selecting a target including genes, genomic flanking regions, RNAs and polypeptide associated with an ailment afflicting the lung airways, obtaining the sequence of a mRNA(s) corresponding to the target gene(s) and/or their genomic flanking region(s) and/or the juxta-membrane regions thereof, and mRNA(s) encoding the target polypeptide(s), selecting at least one segment of the mRNA(s), and synthesizing one or more anti-sense oligonucleotide(s) to the selected mRNA segment(s), and substituting, if necessary, a universal base(s) for one or more A to reduce the proportion of A present in the oligonucleotide to less than 15%.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

This invention arose from a desire by the inventor to improve on his own prior discovery that anti-sense oligonucleotides (oligos) may be utilized therapeutically in the treatment of diseases or conditions which impair respiration, cause inflammation, constrict bronchial tissue or the lung airways, or otherwise impede normal breathing. The inventor reasoned that he could improve on his prior discovery that anti-sense oligos targeted to genes associated with such ailments could effectively treat and prevent the effects and symptomatology of such disease(s) or condition(s). The present invention is premised on the recent discovery by the inventor that oligonucleotides are metabolized in vivo to their deoxynucleotides. In the case of adenosine (A)-containing oligonucleotides, there is break down with release of deoxyadenosine which, in turn, activates adenosine receptors causing bronchoconstriction, inflammation and the like.

The present technology relies on the design of anti-sense oligos targeted to mRNAs associated with ailments involving lung airway pathology(ies), and on their modification to reduce the occurrence of undesirable side effects caused by their release of adenosine upon breakdown, while preserving their activity and efficacy for their intended purpose. In this manner, the inventor targets a specific gene to design one or more anti-sense oligonucleotide(s) (oligos) that selectively bind(s) to the corresponding mRNA, and then reduces, if necessary, their content of adenosine via substitution with universal base or an adenosine analog incapable of activating adenosine A_1, A_{2b} or A_3 receptors. Based on his prior experience in the field, the inventor reasoned that in addition to Adownregulating@ specific genes, he could increase the effect of the agent(s) administered by either selecting segments of RNA that are devoid, or have a low content, of thymidine (T) or, alternatively, substitute one or more adenosine(s) present in the designed oligonucleotide(s) with other nucleotide bases, so called universal bases, which bind to thymidine but lack the ability to activate adenosine receptors and otherwise exercise the constricting effect of adenosine in the lungs, etc. Given that adenosine (A) is a nucleotide base complementary to thymidine (T), when a T appears in the RNA, the anti-sense oligo will have an A at the same position. For consistency's sake, all RNAs and oligonucleotides are represented in this patent by a single strand in the 5' to 3' direction, when read from left to right, although their complementary sequence(s) is (are) also encompassed within the four corners of the invention. In addition, all nucleotide bases and amino acids are represented utilizing the recommendations of the IUPAC-IUB Biochemical Nomenclature Commission, or by the known 3-letter code (for amino acids).

The method of the present invention may be used to treat ailments associated with reduced airway function in a subject, whatever its cause. The adenosine content of the anti-sense agent(s) of the invention have a reduced A content to prevent its liberation upon in vivo degradation of the agent(s). Examples of airway diseases that may be treated by the method of the present invention include cystic fibrosis, asthma, pulmonary hypertension and vasoconstriction, chronic obstructive pulmonary disease (COPD), chronic bronchitis, respiratory distress syndrome, lung cancer and lung metastatic cancers and other airway diseases, including those with inflammatory response.

Anti-sense oligos to the adenosine A_1, A_{2a}, A_{2b}, and A_3 receptors, CCR3 (chemokine receptors), bradykinin 2B, CAM (vascular cell adhesion molecule), and eosinophil receptors, among others, have been shown to be effective in down-regulating the expression of their genes. Some of these act to alleviate the symptoms or reduce respiratory ailments and/or inflammation, for example, by Adown regulation@ of the adenosine A_1, A_{2a}, A_{2b}, and/or A_3 receptors and CCR3, bradykinin 2B, VCAM (vascular cell adhesion molecule) and eosinophil receptors. These agents are preferably administered directly into the respiratory system, e.g., by

inhalation or other means, so that they may reach the lungs without widespread systemic dissemination. This permits the use of substantially lower doses of the agent of the invention as compared with those administered by the prior art, systemically or by other generalized routes and, consequently, reduce undesirable side effects resulting from the agent's widespread distribution in the body. The agent(s) of this invention has (have) been shown to reduce the amount of receptor protein expressed by the tissue. These agents, thus, rather than merely interacting with their targets, e.g. a receptor, lower the number of target proteins that other drugs may interact with. In this manner, the present agent(s) afford(s) extremely high efficacy with low toxicity.

The adenosine receptors discussed above are mere examples of the high power of the inventor's technology. In fact, a large number of genes may be targeted in a similar manner by the present agent(s), to reduce or down-regulate protein expression. By means of example, if the target disease or condition is one associated with impeded or reduced breathing, bronchoconstriction, chronic bronchitis, pulmonary bronchoconstriction and/or hypertension, chronic obstructive pulmonary disease (COPD), allergy, asthma, cystic fibrosis, respiratory distress syndrome, cancers, which either directly or by metastasis afflict the lung, the present method may be applied to a list of potential target mRNAs, which includes the targets listed in Table 1 below, among others.

Table 1: **Pulmonary Disease or Condition (Asthma/Inflammation) Targets**

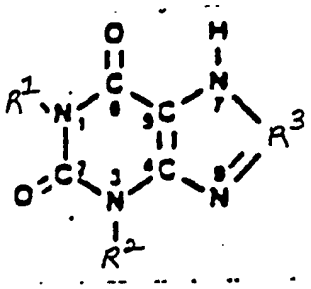
Nf6B Transcription Factor	Interleukin-8 Receptor (IL-8 R)
Interleukin-5 Receptor (IL-5R)	Interleukin-4 Receptor (IL-4R)
Interleukin-3 Receptor (IL-3R)	Interleukin-1beta (IL-1beta)
Interleukin-1β Receptor (IL-1beta R)	Eotaxin
Tryptase	Major Basic Protein
β2-adrenergic Receptor Kinase	Endothelin Receptor A
Endothelin Receptor B	Preproendothelin
Bradykinin B2 Receptor (B2BR)	IgE (High Affinity Receptor)
Interleukin-1 (IL-1)	Interleukin 1 Receptor (IL-1 R)
Interleukin-9 (IL-9)	Interleukin-9 Receptor (IL-9 R)
Interleukin-11 (IL-11)	Interleukin-11 Receptor (IL-11 R)
Inducible Nitric Oxide Synthase	Cyclooxygenase (COX)
Intracellular Adhesion Molecule 1 (ICAM-1)	Vascular Cellular Adhesion Molecule (VCAM)
Rantes	Endothelial Leukocyte Adhesion Molecule (ELAM-1)
Cyclooxygenase-2 (COX-2)	GM-CSF, Endothelin-1
Monocyte Activating Factor	Neutrophil Chemotactic Factor
Neutrophil Elastase	Defensin 1,2,3
Muscarinic Acetylcholine Receptors	Platelet Activating Factor
Tumor Necrosis Factor α	5-lipoxygenase
Phosphodiesterase IV	Substance P
Substance P Receptor	Histamine Receptor
Chymase	CCR-1 CC Chemokine Receptor
Interleukin-2 (IL-2)	Interleukin-4 (IL-4)
Interleukin-12 (IL-12)	Interleukin-5 (IL-5)
Interleukin-6 (IL-6)	Interleukin-7 (IL-7)
Interleukin-8 (IL-8)	Interleukin-12 Receptor (IL-12R)
Interleukin-7 Receptor (IL-7R)	Interleukin-1 (IL-1)
Interleukin-14 Receptor (IL-14R)	Interleukin-14
CCR-2 CC Chemokine Receptor	CCR-3 CC Chemokine Receptor
CCR-4 CC Chemokine Receptor	CCR-5 CC Chemokine Receptor
Prostanoid Receptors	GATA-3 Transcription Factor
Neutrophil Adherence Receptor	MAP Kinase
Interleukin-15 (IL-15)	Interleukin-15 Receptor (IL-15R)
Interleukin-11 (IL-11)	Interleukin-11 Receptor (IL-11R)
NFAT Transcription Factors	STAT 4
MIP-1α	MCP-2
MCP-3	MCP-4
Cyclophillin (A, B, etc.)	Phospholipase A2
Basic Fibroblast Growth Factor	Metalloproteinase

CSBP/p38 MAP Kinase	Tryptase Receptor
PDG2	Interleukin-3 (IL-3)
Interleukin-10 (IL-10)	Cyclosporin A - Binding Protein
FK506-Binding Protein	α4β1 Selectin
Fibronectin	α4β7 Selectin
cMad CAM-1	LFA-1 (CD11a/CD18)
PECAM-1	LFA-1 Selectin
C3bi	PSGL-1
E-Selectin	P-Selectin
CD-34	L-Selectin
p150,95	Mac-1 (CD11b/CD18)
Fucosyl transferase	VLA-4
CD-18/CD11a	CD11b/CD18
ICAM2 and ICAM3	C5a
CCR3 (Eotaxin Receptor)	CCR1, CCR2, CCR4, CCR5
LTB-4	AP-1 Transcription Factor
Protein kinase C	Cysteinyl Leukotriene Receptor
Tachykinnen Receptors (tach R)	IκB Kinase 1 & 2
Interleukin-2 Receptor (IL-2R)	(e.g., Substance P, NK-1 & NK-3 Receptors)
STAT 6	c-mas
NF-Interleukin-6 (NF-IL-6)	Interleukin-10 Receptor (IL-10R)
Interleukin-3 (IL-3)	Interleukin-2 Receptor (IL-2R)
Interleukin-13 (IL-13)	Interleukin-12 Receptor (IL-12R)
Interleukin-14 (IL-14)	Interleukin-6 Receptor (IL-6R)
Interleukin-16 (IL-16)	Interleukin-13 Receptor (IL-13R)
Medullasin	Interleukin-16 Receptor (IL-16R)
Adenosine A_1 Receptor (A_1 R)	Tryptase-I
Adenosine A_{2b} Receptor (A_{2b} R)	Adenosine A_3 Receptor (A_3 R)
β Tryptase	
Adenosine A_{2a} Receptor (A_{2a} R)	IgE Receptor β Subunit (IgE R β)
Fc-epsilon receptor CD23 antigen	IgE Receptor α Subunit (IgE R α)
IgE Receptor Fc Epsilon Receptor (IgERFc ζ R)	Substance P Receptor
Histidine decarboxylase	Tryptase-1
Prostaglandin D Synthase	Eosinophil Cationic Protein
Eosinophil Derived Neurotoxin	Eosinophil Peroxidase
Endothelial Nitric Oxide Synthase	Endothelial Monocyte Activating Factor
Neutrophil Oxidase Factor	Cathepsin G
Macrophage Inflammatory Protein-1-Alpha/Rantes Receptor	Interleukin-8 Receptor α Subunit (IL-8 R α)
Endothelin Receptor ET-B	Substance P Endothelin ETA Receptor

Examples of other targets are 5-lipoxygenase, α-Rantes receptor, Cathepsin G, CCR-1 CC Chemokine receptor, CCR-1 CC Chemokine receptor, CCCR-5 CC Chemokine receptor,, CD-11-CD11a, c-Mas, Endothelial Nitric Oxide Synthase, Endothelial receptor ET-B, Endothelin 1, Eosinophil Cationic Proetin, Eosinophil Derived Neurotoxin, Fc-e receptor II (CD 23 Antigen), Histidine Decarboxylase, Interleukin 10 (IL-10), IL-10 receptor, IL-11 receptor, IL-12, IL-12 receptor, IL-13, IL-13 receptor, IL-14 and its receptor, IL-15 and its receptor, IL-16 and its receptor, IL-6 and its receptor, IL-7 and its receptor, Intracellular Adhesion Molecule -2 (ICAM-2), ICAM-3, Medullasin, Neurokinin-3 receptor (NK-3 R), Neutrophil Oxidase Factor, Platelet Activating Factor receptor, Prostaglandin D Synthase, Protein Kinase c, P-Selectin Glycoprotein Ligand 1 (PSGL-1), Tryptase Activated receptor, IL-2 and its receptor, IL-3 and its receptor, IL-4 and its receptor, IL-5 and its receptor, IL-8 and its receptor, IL-9 and its receptor, Intracellular adhesion Molecule-1, Leukocyte Adhesion Glycoprotein, Leukotriene C-4 Synthase, Major Basic Protein, MCP-3, Monocyte Asctuating Factor, Muscarinic Acetylcholine receptors, Neurokinin-1 Receptor, Neutrophil Chemotactic Factor, Neutrophil Elastase, NfKB, Phosphodiesterase IV, Prostaglandin Receptor, P-selectin, Rantes, Stat-1, Stat-2, Stat-3, Substance P and its receptor, Tryptase, Tumor Necrosis Factor A, Vascular Cellular Adhesion Molecule, AP-1 Transcription Factor, Basic Fibroblast Growth Factor, C5a, CCR-2 CC Chemokine Receptor, CSBP-p38 MAP Kinase,

Cyclooxygenase-2 (COX-2), Cyclophilin (A, B, C, and the rest), Cyclosporin A Binding Protein, Cysteinyl Leukotriene Receptor, E-Selectin, Fibronectin, Fusosyl Transferase, GATAS-3 Transcription Factor, Granulocyte-Macrophage Stimulating Factor (GM-CSF), Histamine Receptor, IKB Kinase 1 and 2, nterleukin 7, L-Selectin, Mac-1 (CD11b and CD18), Mad CAM-1, Map Kinase, MCP-4, Metalloproteinase, MIP-1a, Neutrophil Adherence Receptors, NFAT Transcription Factors, NF-Interleukin-6 (NF-IL-6), Pecam-1,Phospholipase A2, Prostanoid Receptors, Stat-4, Stat-6, VLA-4, and others.

The oligos of this invention may be obtained by first selecting fragments of a target nucleic acid having at least 4 contiguous nucleic acids selected from the group consisting of G and C, and then obtaining a first oligonucleotide 4 to 60 nucleotides long which comprises the selected fragment and has a C and G nucleic acid content of up to and including about 15%. The latter step may be conducted by obtaining a second oligonucleotide 4 to 60 nucleotides long comprising a sequence which is anti-sense to the selected fragment, the second oligonucleotide having an adenosine base content of up to and including about 15%. This method may also comprise, when the selected fragment comprises at least one thymidine base, substituting an adenosine base in the corresponding nucleotide of the anti-sense fragment with a universal base selected from the group consisting of heteroaromatic bases which bind to a thymidine base but have antagonist activity and less than about 0.3 of the adenosine base agonist activity at the adenosine A_1, A_{2b} and A_3 receptors, and heteroaromatic bases which have no activity or have an agonist activity at the adenosine A_{2a} receptor. The analogue heteroaromatic bases may be selected from all pyrimidines and purines, which may be substituted by O, halo, NH_2, SH, SO, SO_2, SO_3, COOH and branched and fused primary and secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, arylsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkylaryl, alkenylaryl, alkynylaryl, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, which may be further substituted by O, halo, NH_2, primary, secondary and tertiary amine, SH, SO, SO_2, SO_3, cycloalkyl, heterocycloalkyl and heteroaryl. The pyrimidines and purines may be substituted at all positions as is known in the art, but preferred are those which are substituted at positions 1, 2, 3, 4, 7 and/or 8. More preferred are pyrimidines and purines such as theophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylline, enprofylline and xantine having the chemical formula



wherein R^1 and R^2 are independently H, alkyl, alkenyl or alkynyl and R^3 is H, aryl, dicycloalkyl, dicycloalkenyl, dicycloalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, O-cycloalkyl, O-cycloalkenyl, O-cycloalkynyl, NH_2-alkylamino-ketoxyalkyloxy-aryl, mono and dialkylaminoalkyl-N-alkylamino-SO_2 aryl, among others.

The inventor reduced the adenosine content of the anti-sense oligos corresponding to the thymidines (T) present in the target RNA to less than about 15%, or fully eliminated A from the oligonucleotide sequence as a means for preventing their breakdown products from freeing adenosine into the lung tissue environment and, thereby, aggravating the subject's ailment and/or countering the beneficial effect of the administered agent.

By means of example, the Nf6B transcription factor may be selected as a target, and its mRNA or DNA searched for low thymidine (T) or desthymidine (desT) fragments. Only desT segments of the mRNA or DNA are selected which, in turn, will produce desA anti-sense as their complementary strand. When a number of RNA desT segments are found, the sequence of the anti-sense segments may be deduced. Typically, about 10 to 30 and even larger numbers of desA anti-sense sequences may be obtained. These anti-sense sequences may include some or all desA anti-sense oligonucleotide sequences corresponding to desT segments of the mRNA of the target, such as anyone of those shown in Table 1 above or Table 2 below. When this occurs, the anti-sense oligonucleotides found are said to be 100% A-free. For each of the original desA anti-sense oligonucleotide sequences corresponding to the target gene, e.g. the NF6B transcription factor, typically about 10 to 30 sequences

may be found within the target gene or RNA which have a low content of thymidine (RNA). In accordance with this invention, the selected fragment sequences may also contain a small number of thymidine (RNA) nucleotides within the secondary or tertiary or quaternary sequences. In some cases, a large adenosine content may suffice to render the anti-sense oligonucleotide less active or even inactive against the target. In accordance with this invention, these so called A non-fully desA sequences may preferably have a content of adenosine of less than about 15%, more preferably less than about 10%, and still more preferably less than 5%, and some even less than 2% adenosine. In some instances a higher content of adenosine is acceptable and the oligonucleotides are still active, particularly where the adenosine nucleotide may be Afixed@ or replaced with a AUniversal@ base that may base-pair with similar or equal affinity to two or more of the four nucleotide present in natural DNA: A, G, C, and T. A universal base is defined in this patent as any compound, more commonly an adenosine analogue, having the capacity to hybridize to thymidine, preferably having substantially reduced, or substantially lacking, ability to bind adenosine receptors. Alternatively, adenosine analogs which do not activate adenosine receptors, such as the adenosine A_1, A_{2b} and/or A_3 receptors, most preferably A_1 receptors, may be used. One example of a universal base is α-deoxyribofuranosol-(5-nitroindole), and an artisan will know how to select others. This Afixing@ step generates a further novel sequence, different from the one found in nature, that permits the anti-sense oligonucleotide to bind, preferably equally well, with the target RNA. An example of a universal base is 2-deoxyribosyl-(5-nitroindole). Other examples of universal bases are 3-nitropyrrole-2'-deoxynucleoside, 5-nitro-indole, 2-deoxyribosyl-(5-nitroindole), 2-deoxyribofuranosyl-(5-nitroindole), 2'-deoxyinosine, 2'-deoxynebularine, 6H, 8H-3,4-dihydropyrimido [4,5-c] oxazine-7-one and 2-amino-6-methoxyaminopurine. In addition to the above, Universal bases which may be substituted for any other base although with somewhat reduced hybridization potential, include 3-nitropyrrole 2'-deoxynucleoside 2-deoxyribofuranosyl-(5-nitroindole), 2'-deoxyinosine and 2'-deoxynebularine (Glen Research, Sterling, VA). More specific mismatch repairs may be made using "P" nucleotide, 6H, 8H-3, 4-dihydropyrimido[4,5-c] [1,2] oxazin-7-one, which base pairs with either guanine (G) or adenine (A) and "K" nucleotide, 2-amino-6-methoxyaminopurine, which base pairs with either cytidine (C) or thymidine (T), among others. Others which are known in the art are also suitable. See, for example, Loakes, D. and Brown, D. M., Nucl .Acids Res. 22:4039-4043 (1994); Ohtsuka, E. et al., J. Biol. Chem.260(5):2605-2608 (1985); Lin, P.K.T. and Brown, D. M., Nucleic Acids Res. 20(19):5149-5152 (1992; Nichols, R. et al., Nature 369(6480): 492-493 (1994); Rahmon , M. S. and Humayun, N. Z., Mutation Research 377 (2): 263-8 (1997); Amosova, O., et al., Nucleic Acids Res. 25 (!0): 1930-1934 (1997); Loakes D. & Brown, D. M., Nucleic Acids Res. 22 (20): 4039-4043 (1994), the entire sections relating to universal bases and their preparation and use in nucleic acid binding is inceorporated herein by reference.

When non-fully desT sequences are found in the naturally occurring target, they typically are selected so that about 1 to 3 universal base substitutions will suffice to obtain a 100% AdesA@ anti-sense oligonucleotide. Thus, the present method provides either anti-sense oligonucleotides to different targets which are low in, or devoid of, A content, as well as anti-sense oligonucleotides where one or more adenosine nucleotides, e. g. about 1 to 3, or more, may be Afixed@ by replacement with a AUniversal@ base. Universal bases are known in the art and need not be listed herein. An artisan will know which bases may act as universal bases, and replace them for A.

The present approach to the design of anti-sense oligonucleotide approach is also applicable to a variety of other diseases or conditions, including other inflammatory diseases, such as cystic fibrosis, chronic obstructive pulmonary disease, chronic bronchitis, pulmonary hypertension, cancers, including those which metastasize to the lung, such as breast cancer, colon cancer, respiratory distress syndrome, prostate cancer, pancreatic cancer, kidney cancer, lymphomas, melanomas, hepatocellular carcinomas, etc.

As used herein, the term "treat" or "treating" asthma or other respiratory and inflammatory conditions or diseases refers to a treatment which decreases the likelihood that the subject administered such treatment will manifest symptoms of a respiratory or inflammatory lung disease or other lung conditions. The term "down-regulate" refers to inducing a decrease in production, secretion or availability (and thus a decrease in concentration) of the targeted intracellular protein.

The present invention is concerned primarily with the treatment of vertebrates, and within this group, of mammals, including human and non-human simians, wild and domesticated animals, marine and land animals, household pets, and zoo animals, for example, felines, canines, equines, pachiderms, cetaceans, and still more preferably to human subjects. One particularly suitable application of this technology is for veterinary purposes,

and includes all types of small and large animals in the care of a veterinarian, including wild animals, marine animals, household animals, zoo animals, and the like. Targeted genes and proteins are preferably mammalian, and the sequences targeted are preferably of the same species as the subject being treated. Although in many instances, targets of a different species are also suitable, particularly those segments of the target RNA or gene that display greater than about 45% homology, preferably greater than about 85% homology, still more preferably greater than about 95% homology, with the recipient's sequence. A preferable group of agents is composed of des-A anti-sense oligos. Another preferred group is composed of non-fully desA oligonucleotides, where one or more adenosine bases are replaced with universal bases.

The terms "anti-sense" oligonucleotides generally refers to small, synthetic oligonucleotides, resembling single-stranded DNA, which in this patent are applied to the inhibition of gene expression by inhibition of a target messenger RNA (mRNA). See, Milligan, J. F. et al., J. Med. Chem. 36(14), 1923-1937 (1993), the relevant portion of which is hereby incorporated in its entirety by reference. The present agents inhibit gene expression of target genes, such as those of the adenosine A_1 A_{2a}, A_{2b}, or A_3 receptors, CCR3 (chemical receptor 320, also known as the eotaxin receptor), VCAM (vascular cell adhesion molecule), eonophil receptor, bradykinin 2B receptor, and many others listed in Table 1 above. This is generally attained by hybridization of the anti-sense oligonucleotides to coding (sense) sequences of a targeted messenger RNA (mRNA), as is known in the art. The exogenously administered agents of the invention decrease the levels of mRNA and protein encoded by the target gene and/or cause changes in the growth characteristics or shapes of the thus treated cells. See, Milligan et al. (1993); Helene, C. and Toulme, J. Biochim. Biophys. Acta 1049, 99-125 (1990); Cohen, J. S. D., Ed., Oligodeoxynucleotides as Anti-sense Inhibitors of Gene Expression; CRC Press: Boca Raton, FL (1987), the relevant portion of which is hereby incorporated in its entirety by reference. As used herein, "anti-sense oligonucleotide" is generally a short sequence of synthetic nucleotide that (1) hybridizes to any segment of a mRNA encoding a targeted protein under appropriate hybridization conditions, and which (2) upon hybridization causes a decrease in gene expression of the targeted protein.

The terms Ades-adenosine@ (desA) and Ades-thymidine@ (desT) refer to oligonucleotides substantially lacking either adenosine (desA) or thymidine (desT). In some instances, the des T sequences are naturally occurring, and in others they may result from substitution of an undesirable nucleotide (A) by another one lacking its undesirable activity. In the present context, the substitution is generally accomplished by substitution of A with a Auniversal base@, as is known in the art.

The mRNA sequence of the targeted protein may be derived from the nucleotide sequence of the gene expressing the protein. For example, the sequence of the genomic human adenosine A_1 receptor and that of the rat and human adenosine A_3 receptors are known. See, US Pat. No. 5,320,962; Zhou, F., et al., Proc. Nat'l Acad. Sci. (USA) 89 :7432 (1992); Jacobson, M.A., et al., U.K. Pat. Appl. No. 9304582.1. The sequence of the adenosine A_{2b} receptor gene is also known. See, Salvatore, C. A., Luneau, C. J., Johnson, R. G. and Jacobson, M., Genomics (1995), the relevant portion of which is hereby incorporated in its entirety by reference. The sequences of many of the exemplary target genes are also known. See, GenBank, NIH. The sequences of those genes whose sequences are not yet available may be obtained by isolating the target segments applying technology known in the art. Once the sequence of the gene, its RNA and/or the protein are known, an anti-sense oligonucleotides may be produced according to this invention as described above to reduce the production of the targeted protein in accordance with standard techniques.

In one aspect of this invention, the anti-sense oligonucleotide has a sequence which specifically binds to a portion or segment of an mRNA molecule which encodes a protein associated with a disease or condition associated with impeded breathing, lung inflammation, airway obstruction, bronchitis, and the like. One effect of this binding is to reduce or even prevent the translation of the corresponding mRNA and, thereby, reduce the available amount of target protein in the subject's lung.

In one preferred embodiment of this invention, the phosphodiester residues of the anti-sense oligonucleotide are modified or substituted. Chemical analogs of oligonucleotides with modified or substituted phosphodiester residues, e.g., to the methylphosphonate, the phosphotriester, the phosphorothioate, the phosphorodithioate, or the phosphoramidate, which increase the in vivo stability of the oligonucleotide are particularly preferred. The naturally occurring phosphodiester linkages of oligonucleotides are susceptible to some degree of degradation by cellular nucleases. Many of the residues proposed herein, on the contrary, are highly resistant to nuclease degradation. See Milligan et al., and Cohen, J. S. D., supra. In another preferred

embodiment of the invention, the oligonucleotides may be protected from degradation by adding a "3'-end cap" by which nuclease-resistant linkages are substituted for phosphodiester linkages at the 3' end of the oligonucleotide. See, Tidd, D. M. and Warenius, H.M., Be. J. Cancer 60: 343-350 (1989); Shaw, J.P. et al., Nucleic Acids Res. 19: 747-750 (1991), the relevant section of which are incorporated in their entireties herein by reference. Phosphoramidates, phosphorothioates, and methylphosphonate linkages all function adequately in this manner for the purposes of this invention. The more extensive the modification of the phosphodiester backbone the more stable the resulting agent, and in many instances the higher their RNA affinity and cellular permeation. See Milligan, et al., supra. Thus, the number of residues which may be modified or substituted will vary depending on the need, target, and route of administration, and may be from 1 to all the residues, to any number in between. Many different methods for replacing the entire phosphodiester backbone with novel linkages are known. See, Millikan et al, supra. Preferred backbone analogue residues include phosphorothioate, methylphosphonate, phosphotriester, thioformacetal, phosphorodithioate, phosphoramidate, formacetal boranophosphate, 3'-thioformacetal, 5'-thioether, carbonate, 5'-N-carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite., 2'-O methyl, sulfoxide, sulfide, hydroxylamine, methylene(methylimino) (MMI), and methyleneoxy(methylimino) (MOMI) residues. Phosphorothioate and methylphosphonate-modified oligonucleotides are particularly preferred due to their availability through automated oligonucleotide synthesis. See, Millikan et al, supra. Where appropriate, the agent of this invention may be administered in the form of their pharmaceutically acceptable salts, or as a mixture of the anti-sense oligonucleotide and its salt. In another embodiment of this invention, a mixture of different anti-sense oligonucleotides or their pharmaceutically acceptable slats is administered.

The agents of this invention have the capacity to attenuate the expression of one target mRNA and/or to enhance or attenuate the activity of one pathway. By means of example, the present method may be practiced by identifying all possible deoxyribonucleotide segments which are low in thymidine (T) or deoxynucleotide segments low in adenosine (A) of about 7 or more mononucleotides, preferably up to about 60 mononucleotides, more preferably about 10 to about 36 mononucleotides, and still more preferably about 12 to about 21 mononucleotides, in a target mRNA or a gene, respectively. This may be attained by searching for mononucleotide segments within a target sequence which are low in, or lack thymidine (RNA), a nucleotide which is complementary to adenosine, or that are low in adenosine (gene), that are 7 or more nucleotides long. In most cases, this search typically results in about 10 to 30 such sequences, I. e. naturally lacking or having less than about 40% adenosine, anti-sense oligonucleotides of varying lengths for a typical target mRNA of average length, i. e., about 1800 nucleotides long. Those with high content of T or A, respectively, may be fixed by substitution of a universal base for one or more As.

The agent(s) of this invention may be of any suitable length, including but not limited to, about 7 to about 60 nucleotides long, preferably about 12 to about 45, more preferably up to about 30 nucleotides long, and still more preferably up to about 21, although they may be of other lengths as well, depending on the particular target and the mode of delivery. The agent(s) of the invention may be directed to any and all segments of a target RNA. One preferred group of agent(s) includes those directed to an mRNA region containing a junction between an intron and an exon. Where the agent is directed to an intron/exon junction, it may either entirely overlie the junction or it may be sufficiently close to the junction to inhibit the splicing-out of the intervening exon during processing of precursor mRNA to mature mRNA, e.g. with the 3' or 5' terminus of the anti-sense oligonucleotide being positioned within about, for example, within about 2 to 10, preferably about 3 to 5, nucleotide of the intron/exon junction. Also preferred are anti-sense oligonucleotides which overlap the initiation codon, and those near the 5' and 3' termini of the coding region.

Table 2 below provides a selected number of targets to which the agents of the invention are effectively applied. Others, however, may also be targeted.

Table 2:Cancer Targets

Transforming Oncogenes	Therapy Targets
ras	thymidylate synthetase
src	thymidylate synthetase
myc	dihydrofolate reductase
bcl-2	thymidine kinase
	deoxycytidine kinase
	ribonucleotide reductase

A group of preferred targets for the treatment of cancer are genes associated with any of different types of cancers, or those generally known to be associated with malignancies, whether they are regulatory or involved in the production of RNA and/or proteins. Examples are transforming oncogenes, including, but not limited to, ras, src, myc, and bcl-2, among others. Other targets are those to which present cancer chemotherapeutic agents are directed to, such as various enzymes, primarily, although not exclusively, thymidylate synthetase, dihydrofolate reductase, thymidine kinase, deoxycytidine kinase, ribonucleotide reductase, and the like.

The present technology is particularly useful in the treatment of cancer ailments given that traditional cancer therapies are fraught with the unresolved problem of selectively killing cancer cells while preserving normal living cells from the devastating effects of treatments such as chemotherapy, radiotherapy, and the like. The present technology provides the ability of selectively attenuating or enhancing a desired pathway or target. This approach provides a significant advantage over standard treatments of cancer because it permits the selection of a pathway, including primary, secondary and possibly tertiary targets, which are not generally expressed simultaneously in normal cells. Thus, the present agent may be administered to a subject to cause a selective increase in toxicity within tumor cells that, for instance, express all three targets while normal cells that may expresses only one or two of the targets will be significantly less affected or even spared.

A group of preferred targets for the treatment of cancers are genes associated with different types of cancers, or those generally known to be associated with malignancies, whether they are regulatory or involved in the production of RNA and/or proteins. Examples are transforming oncogenes, including, but not limited to, ras, src, myc, and bcl-2, among others. Other targets are those to which present cancer chemotherapeutic agents are directed to, such as various enzymes, primarily, although not exclusively, thymidylate synthetase, dihydrofolate reductase, thymidine kinase, deoxycytidine kinase, ribonucleotide reductase, and the like.

In one embodiment, at least one of the mRNAs to which the MTA oligo of the invention is targeted encodes a protein such as transcription factors, stimulating and activating factors, intracellular and extracellular receptors and peptide transmitters in general, interleukins, interleukin receptors, chemokines, chemokine receptors, endogenously produced specific and non-specific enzymes, immunoglobulins, antibody receptors, central nervous system (CNS) and peripheral nervous and non-nervous system receptors, CNS and peripheral nervous and non-nervous system peptide transmitters, adhesion molecules, defensines, growth factors, vasoactive peptides and receptors, and binding proteins, among others; or the mRNA is corresponding to an oncogene and other genes associated with various diseases or conditions.

Examples of target proteins are eotaxin, major basic protein, preproendothelin, eosinophil cationic protein, P-selectin, STAT 4, MIP-1α, MCP-2, MCP-3, MCP-4, STAT 6, c-mas, NF-IL-6, cyclophillins, PDG2, cyclosporin A-binding protein, FK5-binding protein, fibronectin, LFA-1 (CD11a/CD18), PECAM-1, C3bi, PSGL-1,CD-34, substance P, p150,95, Mac-1 (CD11b/CD18), VLA-4, CD-18/CD11a, CD11b/CD18, C5a, CCR1, CCR2, CCR4, CCR5, and LTB-4, among others. Others are, however, suitable, as well.

In another embodiment, at least one of the mRNAs to which the MTA oligo is targeted encodes intracellular and extracellular receptors and peptide transmitters such as sympathomimetic receptors, parasympathetic receptors, GABA receptors, adenosine receptors, bradykinin receptors, insulin receptors, glucagon receptors, prostaglandin receptors, thyroid receptors, androgen receptors, anabolic receptors, estrogen receptors, progesterone receptors, receptors associated with the coagulation cascade, adenohypophyseal receptors,

WHAT IS CLAIMED AS NOVEL AND UNOBVIOUS
IN UNITED STATES LETTERS PATENT IS:

1. A pharmaceutical composition, comprising a nucleic acid which comprises an oligonucleotide (oligo) consisting of up to about 15% adenosine (A), and which is effective for alleviating or inhibiting bronchoconstriction, allergy(ies) and/or inflammation, the oligo being anti-sense to a target selected from the group consisting of

target genes and their corresponding mRNAs;

genomic and mRNA flanking regions selected from the group consisting of 3' and 5' intron-exon borders and the juxta-section between coding and non-coding regions; and

all mRNA segments encoding polypeptides associated with a disease(s) or condition(s) afflicting lung airways;

combinations thereof;

pharmaceutically acceptable salts thereof; and

mixtures thereof.

2. The composition of claim 1, wherein the oligo consists of up to about 10% A.

3. The composition of claim 2, wherein the oligo consists of up to about 5% A.

4. The composition of claim 3, wherein the oligo consists of up to about 3% A.

5. The composition of claim 4, wherein the oligo is A-free.

6. The composition of claim 1, wherein the target gene is selected from the group consisting of target genes and mRNAs encoding polypeptides selected from the group consisting of transcription factors, stimulating and activating factors, interleukins, interleukin receptors, chemokines, chemokine receptors, endogenously produced specific and non-specific enzymes, immunoglobulins, antibody receptors, central nervous system (CNS) and peripheral nervous and non-nervous system receptors, CNS and peripheral nervous and non-nervous system peptide transmitters, adhesion molecules, defensines, growth factors, vasoactive peptides and receptors, and binding proteins; and target genes and mRNAs corresponding to oncogenes, and flanking regions and intron and exon borders.

7. The agent of claim 6, wherein the encoded polypeptides are selected from the group consisting of NfκB Transcription Factor, Interleukin-8 Receptor (IL-8 R), Interleukin 5 Receptor (IL-5 R), Interleukin 4 Receptor (IL-4 R), Interleukin 3 Receptor (IL-3 R), Interleukin-1β (IL-1β), Interleukin 1β Receptor (IL- 1β R), Eotaxin, Tryptase, Major Basic Protein, β2-adrenergic Receptor Kinase, Endothelin Receptor A, Endothelin Receptor B, Preproendothelin, Bradykinin B2 Receptor, IgE High Affinity Receptor, Interleukin 1 (IL-1), Interleukin 1 Receptor (IL-1 R), Interleukin 9 (IL-9), Interleukin-9 Receptor (IL-9 R), Interleukin 11 (IL-11), Interleukin-11 Receptor (IL-11 R), Inducible Nitric Oxide Synthase, Cyclooxygenase (COX), Intracellular Adhesion Molecule 1 (ICAM-1) Vascular Cellular Adhesion Molecule (VCAM), Rantes, Endothelial Leukocyte Adhesion Molecule (ELAM-1), Monocyte Activating Factor, Neutrophil Chemotactic Factor, Neutrophil Elastase, Defensin 1, 2 and 3, Muscarinic Acetylcholine Receptors, Platelet Activating Factor, Tumor Necrosis Factor α, 5-lipoxygenase, Phosphodiesterase IV, Substance P, Substance P Receptor, Histamine Receptor, Chymase, CCR-1 CC Chemokine Receptor, CCR-2 CC Chemokine Receptor, CCR-3 CC Chemokine Receptor, CCR-4 CC Chemokine Receptor, CCR-5 CC Chemokine Receptor, Prostanoid Receptors, GATA-3 Transcription Factor, Neutrophil Adherence Receptor, MAP Kinase, Interleukin-9 (IL-9), NFAT Transcription Factors, STAT 4, MIP-1α, MCP-2, MCP-3, MCP-4, Cyclophillins, Phospholipase A2, Basic Fibroblast Growth Factor, Metalloproteinase, CSBP/p38 MAP Kinase, Tryptose Receptor, PDG2, Interleukin-3 (IL-3), Interleukin-1β (IL-1β), Cyclosporin A-Binding Protein, FK5-Binding Protein, α4β1 Selectin, Fibronectin, α4β7 Selectin, Mad CAM-1, LFA-1 (CD11a/CD18), PECAM-1, LFA-1 Selectin, C3bi, PSGL-1, E-Selectin, P-Selectin, CD-34, L-Selectin, p150,95, Mac-1 (CD11b/CD18), Fucosyl transferase, VLA-4, CD-18/CD11a, CD11b/CD18, ICAM2 and ICAM3, C5a, CCR3 (Eotaxin Receptor), CCR1, CCR2, CCR4, CCR5, LTB-4, AP-1 Transcription Factor, Protein kinase C, Cysteinyl Leukotriene Receptor, Tachychinnen Receptors (tach R), IκB Kinase 1 & 2, STAT 6, c-mas and NF-Interleukin-6 (NF-IL-6).

8. The composition of claim 1, wherein at least one A is substituted by a universal base selected from the group consisting of heteroaromatic bases which bind to a thymidine base but have antagonist activity and less than about 0.3 of the adenosine base agonist activity at the adenosine A_1, A_{2b} and A_3 receptors, and heteroaromatic bases which have no activity or have an agonist activity at the adenosine A_{2a} receptor.

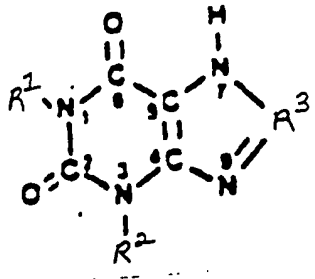
9. The composition of claim 8, wherein all As are substituted by universal bases selected from the group consisting of heteroaromatic bases which bind to a thymidine base but have antagonist activity and less than about 0.3 of the adenosine base agonist activity at the adenosine A_1, A_{2b} and A_3 receptors, and heteroaromatic bases which have no activity or have an agonist activity at the adenosine A_{2a} receptor.

10. The composition of claim 8, wherein the heteroaromatic bases are selected from the group consisting of pyrimidines and purines, which may be substituted by O, halo, NH_2, SH, SO, SO_2, SO_3, COOH and branched and fused primary and secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, arylsulfoxyl,

halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkylaryl, alkenylaryl, alkynylaryl, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, which may be further substituted by O, halo, NH_2, primary, secondary and tertiary amine, SH, SO, SO_2, SO_3, cycloalkyl, heterocycloalkyl and heteroaryl.

11. The composition of claim 10, wherein the pyrimidines and purines are substituted at positions 1, 2, 3, 4, 7 and 8.

12. The composition of claim 11, wherein the pyrimidines and purines are selected from the group consisting of theophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylline, enprofylline and xantine having the chemical formula



wherein R^1 and R^2 are independently H, alkyl, alkenyl or alkynyl and R^3 is H, aryl, dicycloalkyl, dicycloalkenyl, dicycloalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, O-cycloalkyl, O-cycloalkenyl, O-cycloalkynyl, NH_2-alkylamino-ketoxyalkyloxy-aryl and mono and dialkylaminoalkyl-N-alkylamino-SO_2 aryl.

13. The composition of claim 12, wherein the universal base is selected from the group consisting of 3-nitropyrrole-2'-deoxynucleoside, 5-nitro-indole, 2-deoxyribosyl-(5-nitroindole), 2-deoxyribofuranosyl-(5-nitroindole), 2'-deoxyinosine, 2'-deoxynebularine, 6H, 8H-3,4-dihydropyrimido [4,5-c] oxazine-7-one or 2-amino-6-methoxyaminopurine.

14. The composition of claim 1, where a methylated cytocine (^{m}C) is substituted for at least one CpG dinucleotide if present in the oligo(s).

15. The composition of claim 1, wherein at least one nucleotide linking residue of the anti-sense oligonucleotide(s) is a residue selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methyimino), methyleneoxy (methylimino), 2'-O-methyl, phosphoramidate residues and combinations thereof.

16. The agent of claim 15, wherein all nucleotide linking residues are selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methyimino), methyleneoxy (methylimino), 2'-O-methyl, phosphoramidate residues and combinations thereof.

17. The composition of claim 1, wherein the anti-sense oligonucleotide comprises about 7 to 60 mononucleotides.

18. The composition of claim 1, wherein the anti-sense oligonucleotide comprises fragments 1 to 1670 (SEQ ID NOS: 11 through 1680).

19. The composition of claim 1, wherein the anti-sense oligonucleotide is linked to an agent selected from the group consisting of cell internalized or up-taken agent(s) and cell targeting agents.

20. The composition of claim 19, wherein the cell internalized or up taken agent is selected from the group consisting of transferrin, asialoglycoprotein and streptavidin.

21. The composition of claim 19, wherein the nucleic acid is linked to a vector.

22. The vector of claim 21, which comprises a prokaryotic or eukaryotic vector.

23. The composition of claim 1, wherein the oligo is hybridized to a ribonucleic acid.

24. A cell, comprising the agent of claim 1.

25. The composition of claim 1, further comprising a carrier.

26. The composition of claim 25, wherein the carrier comprises a biologically acceptable carrier.

27. The composition of claim 26, wherein the carrier comprises a pharmaceutically or veterinarily acceptable carrier.

28. The composition of claim 25, wherein the carrier is selected from the group consisting of gaseous, liquid, solid carriers and mixtures thereof.

29. The composition of claim 25, further comprising an agent selected from the group consisting of other therapeutic agents, surfactants, antioxidants, flavoring and coloring agents, fillers, volatile oils, buffering agents, dispersants, RNA inactivating agents, anti-oxidants, flavoring agents, propellants and preservatives.

30. The composition of claim 29, comprising the nucleic acid, a surfactant and a carrier.

31. The composition of claim 29, wherein the surfactant is selected from the group consisting of surfactant protein A, surfactant protein B, surfactant protein C, surfactant protein D and surfactant protein and active fragments thereof, non-dipalmitoyl disaturated phosphatidylcholine, dipalmitoylphosphatidylcholine, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, ubiquinones, lysophosphatidylethanolamine, lysophosphatidylcholine, palmitoyl-lysophosphatidylcholin, dehydroepiandrosterone, dolichols, sulfatidic acid, glycerol-3-phosphate, dihydroxyacetone phosphate, glycerol, glycero-3-phosphocholine, dihydroxyacetone, palmitate, cytidine diphosphate (CDP) diacylglycerol, CDP choline, choline, choline phosphate, artificial lamellar bodies vehicles for surfactant components, omega-3 fatty acids, polyenic acid, polyenoic acid, lecithin, palmitic acid, non-ionic ethylene and/or propylene oxide block copolymers, polyoxypropylene, polyoxyethylene, poly (vinyl amine) with dextran and/or alkanoyl side chains, Brij 35, Triton X-100, ALEC, Exosurf, Survant and Atovaquone.

32. The composition of claim 31, wherein the RNA inactivating agent comprises an enzyme, preferably a ribozyme.

33. The composition of claim 1, wherein the anti-sense oligonucleotide is present in an amount of about 0.01 to about 99.99 w/w of the composition.

34. The composition of claim 33, wherein the anti-sense oligonucleotide is present in an amount of about 1 to about 40 w/w of the composition.

35. The composition of claim 34, wherein the anti-sense oligonucleotide is present in an amount of about 5 to about 20 w/w of the composition.

36. A formulation, comprising the composition of claim 25, selected from the group consisting of systemic and topical formulations.

37. The formulation of claim 36, selected from the group consisting of oral, intrabuccal, intrapulmonary, rectal, intrauterine, intratunor, intracranial, nasal, intramuscular, subcutaneous, intravascular, intrathecal, inhalable, transdermal, intradermal, intracavitary, implantable, iontophoretic, ocular, vaginal, intraarticular, otical, intravenous, intramuscular, intraglandular, intraorgan, intralymphatic, implantable, slow release and enteric coating formulations.

38. The formulation of claim 37, which is an oral formulation, wherein the carrier is selected from the group consisting of solid and liquid carriers.

39. The oral formulation of claim 38, wherein the liquid carrier is selected from the group consisting of solutions, suspensions, and oil-in-water and water-in-oil emulsions.

40. The oral formulation of claim 38, which is selected from the group consisting of a powder, dragees, tablets, capsules, sprays, aerosols, solutions, suspensions and emulsions.

41. The formulation of claim 36, which is a topical formulation, wherein the carrier is selected from the group consisting of creams, gels, ointments, sprays, aerosols, patches, solutions, suspensions and emulsions.

42. The formulation of claim 36, which is an injectable formulation, wherein the carrier is selected from the group consisting of aqueous and alcoholic solutions and suspensions, oily solutions and suspensions and oil-in-water and water-in-oil emulsions.

43. The formulation of claim 36, which is a rectal formulation in the form of a suppository.

44. The formulation of claim 36, which is a transdermal formulation, wherein the carrier is selected from the group consisting of aqueous and alcoholic solutions, oily solutions and suspensions and oil-in-water and water-in-oil emulsions.

45. The transdermal formulation of claim 36, which is an iontophoretic transdermal formulation, wherein the carrier is selected from the group consisting of aqueous and alcoholic solutions, oily solutions and suspensions and oil-in-water and water-in-oil emulsions, and wherein the formulation further comprises a transdermal transport promoting agent.

46. An implantable capsule or cartridge, comprising the formulation of claim 44.

47. The formulation of claim 36, wherein the carrier is selected from the group consisting of aqueous and alcoholic solutions and suspensions, oily solutions and suspensions and oil-in-water and water-in-oil emulsions.

48. The formulation of claim 36, wherein the carrier comprises a hydrophobic carrier.

49. The formulation of claim 48, wherein the carrier comprises lipid vesicles or particles.

50. The formulation of claim 49, wherein the vesicles comprise liposomes, and the particles comprise microcrystals.

51. The formulation of claim 50, wherein the vesicles comprise liposomes which comprise the anti-sense oligonucleotide.

52. The formulation of claim 49, wherein the vesicles comprise N-(1-[2, 3-dioleoxyloxi] propyl) - N,N,N- trimethyl- ammonium methylsulfate.

53. The formulation of claim 36, comprising a respirable or inhalable formulation.

54. The respirable or inhalable formulation of claim 53, comprising an aerosol.

55. The formulation of claim 36, in single or multiple unit form.

56. The formulation of claim 36, in bulk.

57. A kit, comprising

a delivery device;

in a separate container, the formulation of claim 36; and

instructions for adding a carrier and for use of the formulation.

58. The kit of claim 57, wherein the delivery device comprises a nebulizer which delivers single metered doses of the formulation.

59. The kit of claim 58, wherein

the nebulizer comprises an insufflator; and

the composition is provided in a piercable or openable capsule or cartridge.

60. The kit of claim 58, wherein

the delivery device comprises a pressurized inhaler; and

the composition comprises a suspension, solution or dry formulation of the agent.

61. The kit of claim 57, further comprising, in a separate container, an agent selected from the group consisting of other therapeutic agents, surfactants, anti-oxidants, flavoring agents, fillers, volatile oils, dispersants, antioxidants, propellants, preservatives, buffering agents, RNA inactivating, cell-internalized or up-taken agents and coloring agents.

62. The kit of claim 61, comprising, in separate containers, a nucleic acid, a surfactant and a carrier.

63. The kit of claim 61, wherein the solvent is selected from the group consisting of organic solvents and organic solvents mixed with one or more co-solvents.

64. The kit of claim 57, wherein the composition is provided in a capsule or cartridge.

65. An in vivo method of delivering a nucleic acid comprising an anti-sense oligonucleotide (oligo) to a target polynucleotide associated with a disease(s) or condition(s) afflicting lung airways, comprising administering to a subject the composition of claim 1 comprising an amount of the nucleic acid effective to reach the target polynucleotide.

66. The method of claim 65, wherein the composition is administered into the subject's respiratory system.

67. The method of claim 65, wherein the agent is administered directly into the subject's lung (s).

68. The method of claim 65, wherein the amount of the agent is effective to bind to the nucleic acid.

69. The method of claim 65, wherein the agent is effective to reduce the production or availability, or to increase the degradation, of the target mRNA or to reduce the amount of the target polypeptide present in the lungs.

70. The method of claim 65, wherein the agent is administered as a respirable aerosol.

71. The method of claim 65, wherein the disease or condition is associated with obstruction of the subject's airways.

72. The method of claim 71, wherein the disease or condition is associated with asthma.

73. The method of claim 65, wherein the disease or condition is associated with inflammation.

74. The method of claim 65, wherein the disease or condition is associated with an allergy, and the target is selected from the group consisting of immunoglobulins and antibody receptors, genes and mRNAs encoding them, their genomic and mRNA flanking sequences and exon and intron borders of the gene (s) and mRNA(s).

75. The method of claim 65, wherein the disease or condition is associated with a malignancy or cancer, and the mRNA encodes a target selected from the group consisting of immunoglobulins and antibody receptors, genomic flanking sequences and genes and mRNAs encoding them and oncogenes.

76. The method of claim 65, wherein the composition is administered by a transdermal or systemic route.

77. The method of claim 76, wherein the composition is administered orally, intracavitarily, intranasally, intraanally, intravaginally, intrauterally, intraarticularly, transdermally, intrabucally, intravenously, subcutaneously, intramuscularly, intravascularly, intratumorously, intraglandularly, intraocularly, intracranial, into an organ, intravascularly, intrathecally, intralymphatically, intraotically, by implantation, by inhalation, intradermally, intrapulmonarily, intraotically, by slow release, by sustained release and by a pump.

78. The method of claim 65, wherein the subject is a mammal.

79. The method of claim 78, wherein the mammal is selected from the group consisting of humans and animals.

80. The method of claim 79, wherein the mammal is a human.

81. The method of claim 79, wherein the subject is an animal.

82. The method of claim 65, wherein the anti-sense oligonucleotide is administered in amount of about 0.005 to about 150 mg/kg body weight.

83. The method of claim 82, wherein the anti-sense oligonucleotide is administered in an amount of about 0.01 to about 75 mg/kg body weight.

84. The method of claim 83, wherein the anti-sense oligonucleotide is administered in an amount of about 1 to 50 mg/kg body weight.

85. The method of claim 65, which is a prophylactic method.

86. The method of claim 65, which is a therapeutic method.

87. The method of claim 65, wherein the oligo is obtained by

(a) selecting fragments of a target nucleic acid having at least 4 contiguous nucleic acids selected from the group consisting of G and C;

(b) obtaining a first oligonucleotide 4 to 60 nucleotides long which comprises the selected fragment and has a C and G nucleic acid content of up to and including about 15%; and

(c) obtaining a second oligonucleotide 4 to 60 nucleotides long comprising a sequence which is anti-sense to the selected fragment, the second oligonucleotide having an A base content of up to and including about 15%.

88. The method of claim 61, wherein the oligo consists of up to about 10% A.

89. The method of claim 88, wherein the oligo consists of up to about 5% A.

90. The method of claim 88, wherein the oligo consists of up to about 3% A.

91. The method of claim 92, wherein the oligo is A-free.

92. The method of claim 65, wherein the target is selected from the group consisting of genes and mRNAs encoding polypeptides selected from the group consisting of transcription factors, stimulating and activating factors, interleukins, interleukin receptors, chemokines, chemokine receptors, endogenously produced specific and non-specific enzymes, immunoglobulins, antibody receptors, central nervous system (CNS) and peripheral nervous and non-nervous system receptors, CNS and peripheral nervous and non-nervous system peptide transmitters, adhesion molecules, defensines, growth factors, vasoactive peptides, peptide receptors and binding proteins; and

genes and mRNAs corresponding to oncogenes.

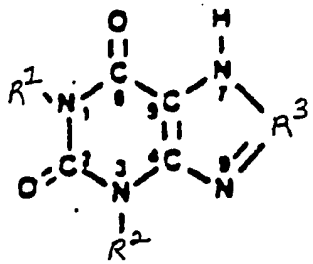
93. The method of claim 65, wherein at least one A is substituted by a universal base selected from the group consisting of heteroaromatic bases which bind to a thymidine base but have antagonist activity and less than about 0.3 of the adenosine base agonist activity at the adenosine A_1, A_{2b} and A_3 receptors, and heteroaromatic bases which have no activity or have an agonist activity at the adenosine A_{2a} receptor.

94. The method of claim 93, wehrein all As are substituted by universal bases selected from the group consisting of heteroaromatic bases which bind to a thymidine base but have antagonist activity and less than about 0.3 of the adenosine base agonist activity at the adenosine A_1, A_{2b} and A_3 receptors, and heteroaromatic bases which have no activity or have an agonist activity at the adenosine A_{2a} receptor.

95. The method of claim 95, wherein the heteroaromatic bases are selected from the group consisting of pyrimidines and purines, which may be substituted by O, halo, NH_2, SH, SO, SO_2, SO_3, COOH and branched and fused primary and secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, arylsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkylaryl, alkenylaryl, alkynylaryl, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, which may be further substituted by O, halo, NH_2, primary, secondary and tertiary amine, SH, SO, SO_2, SO_3, cycloalkyl, heterocycloalkyl and heteroaryl.

96. The method of claim 95, wherein the pyrimidines and purines are substituted at positions 1, 2, 3, 4, 7 and 8.

97. The method of claim 96, wherein the pyrimidines and purines are selected from the group consisting of theophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylline, enprofylline and xantine having the chemical formula



wherein R^1 and R^2 are independently H, alkyl, alkenyl or alkynyl and R^3 is H, aryl, dicycloalkyl, dicycloalkenyl, dicycloalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, O-cycloalkyl, O-cycloalkenyl, O-cycloalkynyl, NH_2-alkylamino-ketoxyalkyloxy-aryl and mono and dialkylaminoalkyl-N-alkylamino-SO_2 aryl.

98. The method of claim 97, wherein the universal base is selected from the group consisting of 3-nitropyrrole-2'-deoxynucleoside, 5-nitro-indole, 2-deoxyribosyl-(5-nitroindole), 2-deoxyribofuranosyl-(5-nitroindole), 2'-deoxyinosine, 2'-deoxynebularine, 6H, 8H-3,4-dihydropyrimido [4,5-c] oxazine-7-one or 2-amino-6-methoxyaminopurine.

99. The method of claim 65, further comprising methylating at least one cytocine (mC) if a CpG dinocleotide if present in the oligo(s).

100. The method of claim 65, further comprising substituting at least one nucleotide linking residue of the anti-sense oligonucleotide(s) with a residue selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methyimino), methyleneoxy (methylimino), 2'-O-methyl, phosphoramidate residues, and combinations thereof.

101. The method of claim 100, wherein all nucleotide linking residues of the oligo are substituted.

102. The method of claim 65, further comprising linking the anti-sense oligonucleotide to an agent selected from the group consisting of cell internalized and up-taken agent(s) and cell targeting agents.

103. The method of claim 102, wherein the cell internalized or up taken agent is selected from the group consisting of transferrin, asialoglycoprotein, and streptavidin.

104. The method of claim 102, wherein the cell targeting agent is a vector.

105. The method of claim 104, wherein the vector to which the agent is operatively linked is a prokaryotic or eukaryotic vector.

106. A method of identifying segments in a target polynucleotide suitable for constructing oligonucleotides which are anti-sense to the target polynucleotide and have an adenosine (A) content of up to and including about 15% of all nucleotides, comprising

(a) selecting fragments of a target polynucleotide acid having at least 4 contiguous nucleic acids selected from the group consisting of G and C; and

(a) obtaining a first oligonucleotide 4 to 60 nucleotides long which comprises the selected fragment and has a C and G content of up to and including about 15%.

107. A method of obtaining oligonucleotides which are anti-sense to a target polynucleotide and have an adenosine content of 0 to up to and including about 15%, comprising conducting the method of claim 106; wherein the first oligonucleotide comprises a sequence which is anti-sense to the selected fragment and has an A content of up to and including about 15%.

108. The method of claim 107, further comprising, when the anti-sense fragment comprises at least one A, substituting at least one A with a universal base selected from the group consisting of

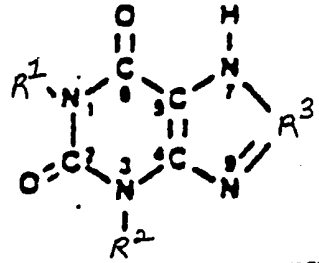
heteroaromatic bases which bind to thymidine (T) but have less than about 0.3 of A's adenosine A_1, A_{2b} and A_3 receptor agonist activity; and

heteroaromatic bases which have no activity or have adenosine A_{2a} receptor agonist activity.

109. The method of claim 108, wherein the heteroaromatic bases are selected from the group consisting of pyrimidines and purines, which may be substituted by O, halo, NH_2, SH, SO, SO_2, SO_3, COOH and branched and fused primary and secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, arylsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkylaryl, alkenylaryl, alkynylaryl, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, which may be further substituted by O, halo, NH_2, primary, secondary and tertiary amine, SH, SO, SO_2, SO_3, cycloalkyl, heterocycloalkyl and heteroaryl.

110. The method of claim 109, wherein the pyrimidines and purines are substituted at positions 1, 2, 3, 4, 7 and 8.

111. The method of claim 109, wherein the pyrimidines and purines are selected from the group consisting of theophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylline, enprofylline and xantine having the chemical formula



wherein R^1 and R^2 are independently H, alkyl, alkenyl or alkynyl and R^3 is H, aryl, dicycloalkyl, dicycloalkenyl, dicycloalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, O-cycloalkyl, O-cycloalkenyl, O-cycloalkynyl, NH_2-alkylamino-ketoxyalkyloxy-aryl and mono and dialkylaminoalkyl-N-alkylamino-SO_2 aryl.

112. The method of claim 108, wherein the universal base is selected from the group consisting of 3-nitropyrrole-2'-deoxynucleoside, 5-nitro-indole, 2-deoxyribosyl-(5-nitroindole), 2-deoxyribofuranosyl-(5-nitroindole), 2'-deoxyinosine, 2'-deoxynebularine, 6H, 8H-3,4-dihydropyrimido [4,5-c] oxazine-7-one or 2-amino-6-methoxyaminopurine.

113. A method of treating a disease or condition associated with a target selected from the group consisting of proteins, gene (s) and their corresponding mRNA(s) encoding the proteins, the genes and mRNA flanking regions and their intron and exon borders, associated with a disease or condition afflicting lung airways, comprising administering to a subject afflicted with the disease or condition the composition of claim 1 comprising an anti-bronchoconstriction, anti-allergic and/or anti-inflammatory effective amount of the nucleic acid.

114. The method of claim 113, wehrein the amount of nucleic acid administered is effective to reduce the production or availability, or to increase the degradation, of the mRNA, or to reduce the amount of the polypeptide present in the lungs.

115. The method of claim 113, wherein the nucleic acid is administered directly to the lung (s) of the subject.

116. The method of claim 113, wherein the nucleic acid is administered as a respirable aerosol.

117. The method of claim 113, wherein the disease or condition is a disease or condition afflicting the lung (s).

118. The method of claim 117, wherein the disease or condition is associated with obstruction of the subject's airways.

119. The method of claim 117, wherein the disease or condition is associated with asthma.

120. The method of claim 117, wherein the disease or condition is associated with inflammation.

121. The method of claim 113, wherein the disease or condition is associated with allergy (ies), and the target is selected from the group consisting of immunoglobulins and antibody receptors, gene(s) and corresponding mRNA(s) encoding them, the genes and mRNA flanking regions and intron and exon borders.

122. The method of claim 113, wherein

the disease or condition is associated with a malignancy or cancer; and

the target is selected from the group consisting of immunoglobulins and antibody receptors, gene(s) and mRNA(s) encoding them, gene(s) and mRNA(s) associated with oncogenes, genomic and mRNA flanking regions and exon and intron borders.

123. The method of claim 113, wherein the composition is administered by a topical or systemic route.

124. The method of claim 123, wherein the composition is administered orally, intracavitarily, intranasally, intraanally, intravaginally, intrauterally, intraarticularly, intraotically, intralymphatically, transdermally, intrabucally, intravenously, subcutaneously, intramuscularly, intratumorously, intraglandularly, intraocularly, intracranial, into an organ, intravascularly, intrathecally, by implantation, by inhalation, intradermally, intrapulmonarily, into the ear, by slow release, by sustained release and by a pump.

125. The method of claim 124, wherein the subject is a mammal.

126. The method of claim 125, wherein the mammals are selected from the group consisting of humans and animals.

127. The method of claim 113, wherein the anti-sense oligonucleotide is administered in amount of about 0.005 to about 150 mg/kg body weight.

128. The method of claim 127, wherein the anti-sense oligonucleotide is administered in an amount of about 0.01 to about 75 mg/kg body weight.

129. The method of claim 130, wherein the anti-sense oligonucleotide is administered in an amount of about 1 to about 50 mg/kg body weight.

130. The method of claim 113, which is a prophylactic method.

131. The method of claim 113, which is a therapeutic method.

132. A method of producing anti-sense oligonucleotide(s) (oligos) consisting of up to and including about 15% adenosine (A), comprising

selecting a target from the group consisting of polypeptides associated with a disease(s) and/or condition(s) afflicting lung airways, genes and RNAs encoding them, the genomic and mRNA flanking regions and the gene(s) and mRNA(s) intron and exon borders;

obtaining the sequence of a mRNA(s) selected from the group consisting of mRNAs corresponding to the target gene(s) and mRNAs encoding the target polypeptide(s), genomic and mRNA flanking regions and the genes and mRNAs intron and exon borders;

selecting at least one segment of the mRNA(s);

synthesizing one or more oligo anti-sense to the selected mRNA segment(s); and

substituting, if necessary, a universal base(s) for one or more A(s) to reduce the content of A present in the oligo to up to about 15% of all nucleotides.

133. The method of claim 132, wherein the universal base is selected from the group consisting of heteroaromatic bases which bind to a thymidine base but have antagonist activity and less than about 0.3 of the adenosine base agonist activity at the adenosine A_1, A_{2b} and A_3 receptors, and heteroaromatic bases which have no activity or have an agonist activity at the adenosine A_{2a} receptor.

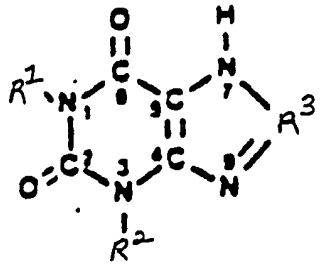
134. The method of claim 132, wherein all As are substituted with universal bases selected from the group consisting of heteroaromatic bases which bind to a thymidine base but have antagonist activity and less than

about 0.3 of the adenosine base agonist activity at the adenosine A_1, A_{2b} and A_3 receptors, and heteroaromatic bases which have no activity or have an agonist activity at the adenosine A_{2a} receptor.

135. The method of claim 133, wherein the heteroaromatic bases are selected from the group consisting of pyrimidines and purines, which may be substituted by O, halo, NH_2, SH, SO, SO_2, SO_3, COOH and branched and fused primary and secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, arylsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkylaryl, alkenylaryl, alkynylaryl, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, which may be further substituted by O, halo, NH_2, primary, secondary and tertiary amine, SH, SO, SO_2, SO_3, cycloalkyl, heterocycloalkyl and heteroaryl.

136. The method of claim 135, wherein the pyrimidines and purines are substituted at positions 1, 2, 3, 4, 7 and 8.

137. The method of claim 135, wherein the pyrimidines and purines are selected from the group consisting of theophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylline, enprofylline and xantine having the chemical formula



wherein R^1 and R^2 are independently H, alkyl, alkenyl or alkynyl and R^3 is H, aryl, dicycloalkyl, dicycloalkenyl, dicycloalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, O-cycloalkyl, O-cycloalkenyl, O-cycloalkynyl, NH_2-alkylamino-ketoxyalkyloxy-aryl and mono and dialkylaminoalkyl-N-alkylamino-SO_2 aryl.

138. The method of claim 135, wherein the universal base is selected from the group consisting of 3-nitropyrrole-2'-deoxynucleoside, 5-nitro-indole, 2-deoxyribosyl-(5-nitroindole), 2-deoxyribofuranosyl-(5-nitroindole), 2'-deoxyinosine, 2'-deoxynebularine, 6H, 8H-3,4-dihydropyrimido [4,5-c] oxazine-7-one or 2-amino-6-methoxyaminopurine.

139. The method of claim 132, wherein the proportion of A in the oligo is reduced to up to about 10%.

140. The method of claim 139, wherein the proportion of A in the oligo is reduced to up to about 5%.

141. The method of claim 140, wherein the proportion of A in the oligo is reduced to up to about 3%.

142. The method of claim 141, wherein the proportion of A in the oligo is reduced to about 0.

143. The method of claim 139, wherein the selected segment contains less than about 15% T.

144. The method of claim 132, further comprising substituting a methylated cytosine for cytosine in at least one CpG dinucleotide present in the anti-sense oligo(s).

145. The method of claim 132, wherein the anti-sense oligo(s) are about 7 to about 60 nucleotides long.

146. The method of claim 132, wherein the target is selected from the group consisting of transcription factors, stimulating and activating factors, interleukins, interleukin receptors, chemokines, chemokine receptors, endogenously produced specific and non-specific enzymes, immunoglobulins, antibody receptors, central nervous system (CNS) and peripheral nervous and non-nervous system receptors, CNS and peripheral nervous and non-nervous system peptide transmitters, adhesion molecules, selectins, defensines, growth factors, vasoactive peptides, vasoactive peptide receptors, and binding proteins and oncogenes.

147. The method of claim 146, wherein the target genes are selected from the group consisting of oncogenes.

148. An anti-sense oligonucleotide produced by the method of claim 132.